PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

Applicant(s): Robert J. LEVY et al.

Serial No: 09/933,680 Group Art Unit: 1651

Filed: August 22, 2001 Examiner: Sandra E. Saucier

Att. Docket No.: T1118/20031 Confirmation No.: 7085

For: STABILIZATION OF IMPLANTABLE BIOPROSTHETIC DEVICES

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Narendra Vyavahare, Ph.D., a permanent resident of the United States of America and a citizen of India, hereby declare and state:

1. The resume attached as Exhibit A accurately reflects my professional credentials.

2. I am one of the inventors of the above-identified application and currently employed by Clemson University, Clemson, South Carolina.

3. I have reviewed the application, the Office Action of December 2, 2002, and U.S. Patent Nos. 5,891,196 (the '196 patent), 4,378,224 (the '224 patent), and 5,447,536 (the '536 patent). Accordingly, I understand that all of the claims of the present application were rejected over U.S. Patent Nos. 5,891,196 and 4,378,224, and that claims 5-6 have been rejected as being obvious over U.S. Patent Nos. 5,891,196 and 4,378,224 and further in view of U.S. Patent No. 5,447,536.

4. Prior to my invention, it was known in the art to use carbodiimide and glutaraldehyde at an acidic pH of about 5 for fixation of biological tissues as disclosed by the '196 and '224 patents.

5. The '536 patent discloses that cross-linking of a prosthesis tissue can be done in the absence of glutaraldehyde to prevent/retard calcification and can be conducted at a variable pH, preferably in a range from about 6.5 to 7.4 (col. 5, lines 60-67). The '536 patent requires the presence of a coupling agent such as EDC and a coupling enhancer such as sulfo-NHS for the cross-linking of the prosthesis tissue with a cross-linking agent such as carbodiimide. It is significant that the '536 patent does not disclose any particular advantages in using pH from about 6.5 to 7.4.

6. Prior to my invention, nobody appreciated the undesirable effect of low pH on collagen and that using carbodiimide and glutaraldehyde at pH of about 5 (acidic range), which is an optimal range for carbodiimide's reactivity, will cause excessive cross-linking of glycosaminoglycans (GAGs) and thereby a loss of flexibility of a cross-linked implant. We, the inventors, were first to recognize that stabilizing GAGs on a tissue by using carbodiimide at a pH of 6.9 to 7.9 (which is not the optimal range for reactivity purposes) and cross-linking with glutaraldehyde yield a more flexible attachment of GAGs to the implant.

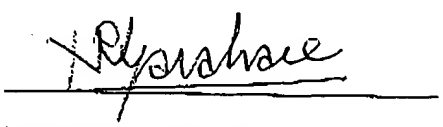
7. One of ordinary skill in the art of stabilizing of implantable bioprosthetic devices (to which the present application pertains) would have lacked any motivation to consult or modify the teachings of the '536 patent regarding the pH to produce the claimed invention, a method of treating an implantable biological tissue, wherein said method comprises (1) stabilizing glycosaminoglycans on the tissue and (2) cross-linking proteins on the tissue, wherein the stabilization of glycosaminoglycans on the tissue comprises contacting the tissue with (a) a water-soluble carbodiimide composition having a pH of 6.9 to 7.9, (b) a carbohydrate oxidizing agent, or (c) a heterofunctional azide reagent, provided that when the stabilizing comprises contacting the tissue with the water-soluble carbodiimide composition, the cross-linking comprises contacting the tissue with glutaraldehyde. One of the reasons for such lack of motivation is that the

'536 patent specifically requires the absence of glutaraldehyde in a combination with carbodiimide.

8. Likewise, such an ordinarily skilled artisan would not have had a reasonable expectation that carbodiimide/glutaraldehyde treatment at pH of 6.9 to 7.9 useful for stabilizing/cross-linking of implantable bioprosthetic devices could be derived from the teachings of the '536 patent. The novel and unexpected properties of implantable bioprosthetic devices made by the method of the present invention are not disclosed or suggested in the '536 patent or in any prior art of which I am aware. Such unexpected properties are disclosed in the present application in Tables I and II. Specifically, glutaraldehyde alone at any pH was not capable of fixing hyaluronic acid (HA), one of the GAGs in the heart valve. However, we discovered that combination of carbodiimide with glutaraldehyde was 3 times more effective in fixing HA than glutaraldehyde alone. As demonstrated in Table II, which shows thermal denaturation temperature data that are directly proportional to the extent of crosslinking in the tissue, the carbodiimide-glutaraldehyde combination was as effective in crosslinking proteins as glutaraldehyde alone (Td 86.4°C and 87°C respectively.). It is evident that carbodiimide alone at the stated pH was not as effective in crosslinking proteins (Td 73.2) as the carbodiimide-glutaraldehyde combination.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

July 15, 2003



Narendra Vyavahare, Ph.D.

EXHIBIT A

RESUME

NAME	POSITION TITLE
NAREN VYAVAHARE	**ASSISTANT PROFESSOR**

EDUCATION *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Pune University, Pune, India	BS	1983	Chemistry
Pune University, Pune India	MS	1985	Organic Chemistry
National Chemical Laboratory (Pune University),India	Ph.D.	1990	Biomaterials
Rutgers University, New Jersey, USA	Post-Doc.	1991-1993	Biomaterials
University of Michigan, Ann Arbor, MI, USA	Senior Post-Doc. Fellow	1993-1994	Biomaterials

RESEARCH AND/OR PROFESSIONAL EXPERIENCE:

Professional Experience

1999-Present	Assistant Professor of Bioengineering, Clemson University, Clemson, SC
1997-1999	Research Assistant Professor, Department of Pediatrics, University of Pennsylvania, and Assistant Scientist, Division of Cardiology, Children's Hospital of Philadelphia, PA
1995-1997	Research Investigator, Department of Pediatrics, University of Michigan

Honors and Awards

1982	Certificate of Merit from Pune University, India at B.S. level (chemistry)
1983-85	Special Certificate of Merit from the Pune University, India at M.S. (organic chemistry)
1986-90	Senior Research Fellowship for Ph.D. from Council of Scientific and Industrial Research, New Delhi, India.
1999	Topic co-ordinator, reviewer soft tissue biomaterials, Biomaterials Society
2000	National American Heart Association Scientist Development Award

Memberships: Society for Biomaterials, American Society of gene therapy, Sigma Xi

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Narendra Vyavahare, Xuan Qu, Priya Behari, Michael Lee, Fredrick Schoen and Robert Levy, "Controlled release polymers for preventing bioprosthetic aortic wall calcification: Synergism of CaEHBP and FeCl3", **J. of C ntroll d Release**, 34, 97-108, 1995.

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